GM-CSF-based treatments in COVID-19: reconciling opposing therapeutic approaches

Lang, Frederick M ; Lee, Kevin M-C ; Teijaro, John R ; Becher, Burkhard ; Hamilton, John A

Abstract: Therapeutics against coronavirus disease 2019 (COVID-19) are urgently needed. Granulocyte-macrophage colony-stimulating factor (GM-CSF), a myelopoietic growth factor and pro-inflammatory cytokine, plays a critical role in alveolar macrophage homeostasis, lung inflammation and immunological disease. Both administration and inhibition of GM-CSF are currently being therapeutically tested in COVID-19 clinical trials. This Perspective discusses the pleiotropic biology of GM-CSF and the scientific merits behind these contrasting approaches.

DOI: https://doi.org/10.1038/s41577-020-0357-7

GM-CSF-based treatments in COVID-19: reconciling opposing therapeutic approaches

Frederick M. Lang, Kevin M.-C. Lee, John R. Teijaro, Burkhard Becher and John A. Hamilton

Abstract | Therapeutics against coronavirus disease 2019 (COVID-19) are urgently needed. Granulocyte–macrophage colony-stimulating factor (GM-CSF), a myelopoietic growth factor and pro-inflammatory cytokine, plays a critical role in alveolar macrophage homeostasis, lung inflammation and immunological disease. Both administration and inhibition of GM-CSF are currently being therapeutically tested in COVID-19 clinical trials. This Perspective discusses the pleiotropic biology of GM-CSF and the scientific merits behind these contrasting approaches.

Coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has turned into a global pandemic. No agent has proved effective against coronavirus infections, and the development of novel therapeutics is critical to solve this public health crisis. Granulocyte–macrophage colony-stimulating factor (GM-CSF), an important myelopoietic growth factor and pro-inflammatory cytokine, has attracted great interest as a therapeutic target in COVID-19. Increased percentages of GM-CSF-expressing leukocytes have been found in the blood of patients with COVID-19 (REF.[1]), and inhibition of GM-CSF has shown benefit in animal studies of many hyperinflammatory conditions[2,3] that are thought to be pathologically similar to late stages of COVID-19. As of 28 May 2020, six companies had initiated randomized controlled clinical trials and open-label studies and/or expanded access/compassionate use programmes assessing the use of monoclonal antibodies (mAbs) to GM-CSF or GM-CSF receptor (GM-CSFR) to treat various stages of COVID-19 (REFS[4–9]). Conversely, GM-CSF plays an important role in alveolar macrophage homeostasis and lung pathogen clearance[2], and investigator-initiated trials are studying the administration of recombinant human GM-CSF (sargramostim) in patients with respiratory failure due to COVID-19.

This Perspective provides a brief overview of the pleiotropic biology of GM-CSF and examines the preclinical and clinical studies supporting the use of both sargramostim and GM-CSF-targeting mAbs in COVID-19.

GM-CSF overview

Role in homeostasis. Macrophage colony-stimulating factor (M-CSF), granulocyte colony-stimulating factor (G-CSF) and GM-CSF are implicated in myelopoiesis, the production of monocytes, macrophages, dendritic cells and granulocytes (neutrophils, eosinophils and basophils) from progenitor cells. M-CSF and G-CSF appear to be involved in steady-state myelopoiesis, given that null mutants of the encoding genes in mice cause severe phenotypes (for example, skeletal and sensory defects and neutropenia)[10–12]. By contrast, GM-CSF is barely detectable in the blood of healthy individuals and is thought to serve less of a role in homeostatic myelopoiesis, as evidenced by the fact that GM-CSF-deficient mice have a virtually normal lifespan and have less dramatic alterations in the basal myeloid system[13,14].

Importantly, however, GM-CSF is known to be a critical homeostatic factor in lung alveoli, where it is produced at low levels for the development and long-term maintenance of alveolar macrophages[15,16]. Severe deficiency of GM-CSF (for example, due to autoantibodies to GM-CSF or mutations that ablate GM-CSFR function) causes pulmonary alveolar proteinosis (PAP), a life-threatening interstitial lung disease in which dysfunctional alveolar macrophages cannot clear surfactant[16]. Patients with PAP have increased susceptibility to opportunistic infections due to defective antimicrobial function of alveolar macrophages and basal circulating neutrophils, caused by impaired GM-CSF signalling[16,17]. In mice, GM-CSF has been reported to be required for the steady-state maintenance of non-lymphoid tissue-resident CD103$^+$ dendritic cells across multiple tissues, and this population of cells was shown to be critically important for the initiation of CD8$^+$ T cell responses in the lung[18,19]. GM-CSF thus serves a crucial role in normal lung health and can be important for host defence.

Role in inflammation. During inflammation, GM-CSF can be secreted by several different cell types, including epithelial cells and leukocytes, and is a critically important cytokine that can drive both innate and adaptive immune responses (FIG. 1). GM-CSFR is mainly expressed on myeloid cells, generally restricting the direct-acting function of GM-CSF to cells of this lineage. GM-CSF broadly serves two important roles during the immune response: it polarizes mature myeloid cells into a pro-inflammatory phenotype (paracrine/autocrine function), and it governs 'emergency myelopoiesis', expanding and mobilizing progenitor myeloid cells to sites of inflammation (endocrine function)[2]. GM-CSF-activated myeloid cells can secrete reactive oxygen species and express elevated levels of pro-inflammatory cytokines (such as IL-1, IL-6 and tumour necrosis factor (TNF)) and a variety of chemokines (such as CCL2, IL-8 and CCL17, which can attract monocytes, neutrophils and lymphocytes, respectively)[2]. GM-CSF can also enhance the ability of dendritic cells to prime T cells during antigen-specific immune responses[14,18]. A distinct subset of CD4$^+$ T helper cells (T_H cells) that produce primarily GM-CSF has been identified[20–23]. These T cells can heighten the immune response by activating pro-inflammatory myeloid cells and recruiting them to sites of inflammation[20–22]. Thus, it has

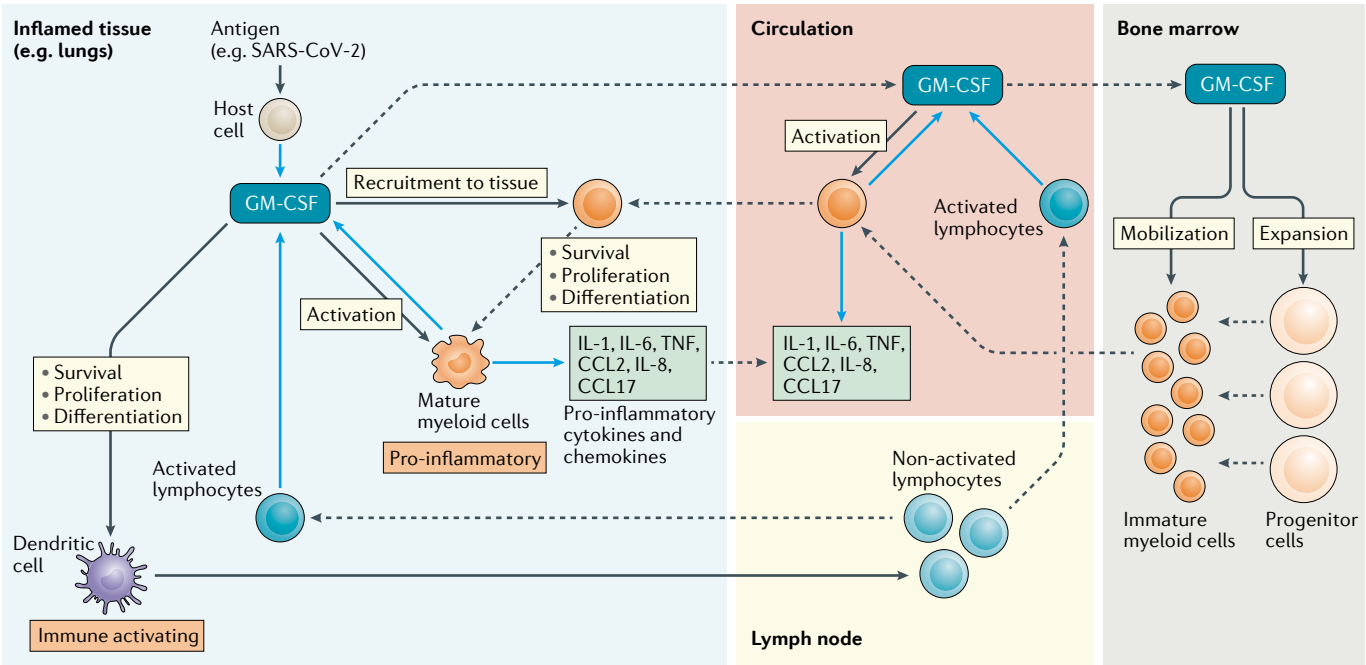

Fig. 1 | **GM-CSF and inflammation.** The immune response, including granulocyte–macrophage colony-stimulating factor (GM-CSF) upregulation, can be triggered when an antigen induces a 'danger' signal from a host cell. During this response, GM-CSF can act locally in inflamed tissue to induce the survival, proliferation and/or differentiation of myeloid cells, such as monocytes/macrophages and neutrophils. More specifically, GM-CSF can potentially do the following: activate mature myeloid cells to a pro-inflammatory phenotype with enhanced cytokine (for example, IL-1, IL-6 and tumour necrosis factor (TNF)) and chemokine (for example, CCL2, IL-8 and CCL17) secretory capacity; recruit immature myeloid cells from the circulation and aid in their terminal differentiation; and develop/stimulate dendritic cells to prime the adaptive immune response. Activated lymphocytes (for example, GM-CSF-producing T helper cells) can migrate into diseased tissue and the circulation, serving as a source of GM-CSF, thereby aiding in the recruitment and activation of new myeloid cells. GM-CSF levels can also be elevated systemically to induce 'emergency myelopoiesis', expanding and mobilizing immature myeloid/progenitor haematopoietic cells in the circulation and bone marrow. These GM-CSF-dependent responses thus heighten the inflammatory response in inflamed or diseased tissue. The broad range of immunological activities of GM-CSF can form part of positive-feedback loops/networks that can initiate and maintain disease-causing hyperactive or chronic immune responses. GM-CSF has also been shown to enhance antimicrobial host defence and lung barrier repair (not shown). Blue arrows mean 'secretes', black arrows mean 'acts on', dotted arrows indicate movement or differentiation and 'host cell' refers to various haematopoietic and non-hematopoietic cell types. SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

been proposed that GM-CSF serves as a primary communication conduit between inflammatory lymphoid and myeloid cells[14].

Role in disease. The aberrant expression of GM-CSF is known to drive excessive inflammation, pain, chemotaxis and tissue damage and to enhance the production of other pathogenic cytokines[2,3]. Given the proposed role of GM-CSF at the interface of lymphoid and myeloid cells, it has been postulated that a 'GM-CSF network' promotes disease by driving inflammatory responses to become persistent or hyperactive[2]. This network is defined as a positive-feedback loop involving the interdependent secretion of GM-CSF and pro-inflammatory cytokines/chemokines across monocytes/macrophages, T_H cells and neighbouring cell populations. The cytokines most prominently implicated in this network are IL-1, IL-6 and TNF[2], which have been targeted successfully in various inflammatory diseases and have now been suggested as potential targets in COVID-19 (REFS[24,25]).

GM-CSF has been shown to be upregulated either systemically and/or in the diseased tissues of patients with autoimmune conditions (such as rheumatoid arthritis)[2,26] as well as in conditions that show similarities to late-stage COVID-19, including severe acute respiratory syndrome (SARS)[27], acute respiratory distress syndrome (ARDS)[28], cytokine release syndrome (CRS)[29], haemophagocytic lymphohistiocytosis (HLH)[30], hyperinflammation associated with graft-versus-host disease (GvHD)[31] and other inflammatory diseases of the lung[32], heart[33–35] and nervous system[21,23,36,37]. GM-CSF-producing T_H cells have been identified as being involved in the pathogenesis of various immunological disorders (for example, rheumatoid arthritis[26], multiple sclerosis[21,22] and sepsis[38]), reminiscent of the pathogenic T_H17 pathway known to drive disease pathology in multiple autoimmune contexts (for example, psoriasis)[39]. GM-CSF inhibition via neutralizing antibodies has shown beneficial effects in a diverse range of preclinical models, including those of many of the aforementioned diseases[3]. In humans, treatment with GM-CSF-targeting mAbs has demonstrated efficacy across multiple phase II clinical trials for rheumatoid arthritis, with some potential advantages (for example, fewer off-target effects and decreased infection susceptibility) over standard-of-care therapeutics, such as disease-modifying antirheumatic drugs, TNF-targeting agents and Janus kinase inhibitors[2,40] (TABLE 1).

GM-CSF-based therapies in COVID-19

COVID-19 clinical course and immunopathogenesis. Although most infections are mild, ~20% of patients with COVID-19 experience severe viral pneumonia that can progress to ARDS and death[41]. On the basis of emerging data, as well as evidence from previous coronavirus

epidemics[42], a three-phase clinical staging model has been proposed for COVID-19: (1) fever, cough and other relatively mild symptoms accompanying an increase in viral load; (2) severe pneumonia that persists, despite a decline in viral load, due to a hyperactive immune response; and (3) continuation of significant immune dysregulation resulting in pulmonary destruction, cardiac instability, multiorgan failure and death[43]. It has become increasingly well appreciated that the characteristic hyperactive immune response driving COVID-19 progression consists of a 'cytokine storm', overwhelming infiltration of inflammatory myeloid cells into the lungs (particularly monocytes, macrophages and neutrophils), and even a disease phenotype resembling secondary HLH (often referred to as 'macrophage activation syndrome')[25,43–47].

A subset of patients also experience acute myocardial injury and/or neuropsychiatric symptoms, which are associated with poor outcomes and may be caused by systemic inflammation[48,49]. Therapies aimed at increasing viral clearance, strengthening lung tissue and/or reducing the excessive host immune response may be able to reduce the morbidity and mortality associated with COVID-19.

Rationale for administering GM-CSF in COVID-19. Recombinant human GM-CSF (sargramostim) is FDA-approved for multiple indications, and its administration may provide several benefits to patients with COVID-19. As mentioned already, GM-CSF is required to maintain pulmonary function and lung sentinel cell-mediated immunity[16,50]. Overexpression of GM-CSF in mice prevented hyperoxia-induced lung injury by strengthening the resistance of alveolar wall cells to apoptosis and protecting against secondary bacterial infection[51,52]. Early elevated expression of GM-CSF in bronchoalveolar lavage fluid (BALF) of patients with acute lung injury and ARDS correlated with increased survival, potentially owing to the enhanced survival of alveolar macrophages[53]. On the basis of these data, a randomized controlled clinical trial was conducted to study the use of intravenously administered recombinant human GM-CSF in patients with acute lung injury or ARDS[54]. This trial failed to demonstrate reduction of ventilator-free days or mortality over the 28-day observation period. However, the study was underpowered owing to a slow recruitment pace ($N = 130$ of planned 200 participants)[54], and it has been hypothesized that local delivery of high

Table 1 | **History and current status of GM-CSF-based therapies undergoing assessment in patients with COVID-19**

Company	Drug	Completed studies[a]	Other indications[a]	Status in COVID-19[a]
GlaxoSmithKline	Otilimab (anti-GM-CSF)	Phase I or II RA (×4) Phase Ib MS Phase IIa hand OA	Phase III RA (ongoing, ×4)	RCT (2 arms, $N = 800$, NCT04376684)
Roivant	Gimsilumab (anti-GM-CSF)	Phase I HVs + RA Phase I HVs	No announcements	RCT (2 arms, $N = 270$, NCT04351243)
Humanigen	Lenzilumab (anti-GM-CSF)	Phase I HVs Phase I CMML Phase II asthma	Phase I/II CAR T cell-related CRS/NT (ongoing) Phase II CMML (planned) Phase II/III GvHD-related CRS (planned) Phase III eosinophilic asthma (planned)	RCT (2 arms, $N = 238$, NCT04351152) Expanded access
I-Mab	TJM2 (anti-GM-CSF)	Phase I HVs	Phase Ib RA (ongoing) Phase II CAR T cell-related CRS/NT (planned)	RCT (3 arms, $N = 144$, NCT04341116)
Kiniksa	Mavrilimumab (anti-GM-CSFR)	Phase I HVs Phase I RA Phase II RA (×3) Phase II RA OLE	Phase II GCA (ongoing) Phase II CAR T cell-related CRS/NT (planned)	RCT (2 arms, $N = 60$, NCT04399980) RCT (2 arms, $N = 50$, NCT04397497) Open-label study
Izana	Namilumab (anti-GM-CSF)	Phase I HVs Phase Ib RA Phase II RA Phase II PsO Phase II axial SpA	Phase III RA (planned)	Expanded access
Partner Therapeutics	Sargramostim (rhuGM-CSF)	FDA-approved for use in multiple indications	Phase I PD (ongoing) Phase II post-transplant recovery (ongoing) Phase II/III melanoma (ongoing) Phase II biliary cancer (ongoing)	RCT (2 arms, $N = 30$, NCT04400929) RCT (open-label study, 2 arms, $N = 80$, NCT04326920)

As of 28 May 2020, six companies had begun a clinical study treating patients with coronavirus disease 2019 (COVID-19) with monoclonal antibodies to granulocyte–macrophage colony-stimulating factor (GM-CSF) or GM-CSF receptor (GM-CSFR). One company is also supporting investigator-initiated trials of recombinant human GM-CSF (rhuGM-CSF) in patients with COVID-19. CAR chimeric antigen receptor; CMML, chronic myelomonocytic leukaemia; CRS, cytokine release syndrome; GCA, giant cell arteritis; GvHD, graft-versus-host disease; HVs, healthy volunteers; MS, multiple sclerosis; NT, neurotoxicity; OA, osteoarthritis; OLE, open-label extension; PD, Parkinson disease; PsO, psoriasis; RA, rheumatoid arthritis; RCT, randomized controlled trial (double-blind unless otherwise stated); SpA, spondyloarthritis; ×3 or ×4, three or four of the indicated trials are ongoing or have been completed. [a]Information obtained from ClinicalTrials.gov or company public announcements.

levels of GM-CSF directly to the lungs may be required for a therapeutic effect[55,56].

Across many preclinical models of viral and bacterial pneumonia, GM-CSF expression in the lung has been shown to serve a beneficial role by enhancing repair of injured lung tissue and by activating innate and adaptive immune responses to clear pathogens[19,50,56–63]. In this context, GM-CSF is thought to act mainly on alveolar macrophages and tissue-resident CD103$^+$ dendritic cells, and there is even evidence that GM-CSF directly modulates alveolar epithelial cells[19,50,64]. Pretreatment with intranasally administered GM-CSF protected mice from lethal influenza-induced lung injury[56,60], and lung-specific overexpression of GM-CSF after influenza viral infection in an inducible transgenic mouse model significantly increased survival[61]. Inhaled GM-CSF also protected against secondary bacterial infection in a postinfluenza pneumococcal pneumonia mouse model[62]. Conversely, GM-CSF-deficient mice showed no survival 48 hours after intratracheal inoculation with Gram-negative bacteria (compared with 100% survival in controls) due to impaired alveolar macrophage bactericidal function[63]. During infection resolution, GM-CSF was shown to mediate macrophage–epithelial cell crosstalk, stimulating alveolar epithelial cell proliferation and barrier repair[64,65]. In six patients with pneumonia-associated ARDS, compared with an external control group, increased oxygenation and lung compliance were observed following treatment with inhaled GM-CSF on a compassionate use basis; however, these results will need to be verified in controlled studies[55]. Currently, a randomized, open-label, investigator-initiated trial is ongoing to assess inhaled and/or intravenously administered sargramostim in patients with acute hypoxic respiratory failure due to COVID-19 ($N = 80$, NCT04326920)[66]. A randomized, double-blind, placebo-controlled study has also been initiated to assess intravenously administered sargramostim in 30 patients with respiratory failure due to COVID-19 (NCT04400929)[66] (TABLE 1). This strategy may prove useful for stabilizing alveolar macrophage and epithelial cell function, increasing SARS-CoV-2 clearance, protecting against secondary infection and contributing to lung repair mechanisms.

Risks associated with GM-CSF administration in COVID-19. Sargramostim is typically used clinically to expand bone marrow progenitor cells and promote myeloid reconstitution, for example, in cases of neutropenia following chemotherapy or autologous bone marrow transplantation. In apparent contradiction to the data presented in the previous subsection, the sargramostim FDA label cautions against treating patients with hypoxia because its administration has been shown to induce respiratory symptoms due to excessive granulocyte mobilization into the lungs from the circulation[67]. It was demonstrated in healthy volunteers that neutrophils primed ex vivo with GM-CSF are sequestered in the pulmonary vasculature, whereas little to no retention was observed with non-primed cells[68]. Considering that neutrophil accumulation in the lung is a hallmark of ARDS[69], it is noteworthy that acute lung injury has been reported as a potential complication of sargramostim use in rare cases[70]. GM-CSF has been shown to boost neutrophil survival in ARDS, and thus inhibition of the GM-CSF pathway has been proposed as a potential ARDS therapeutic approach[17,28,71], contrary to recommendations in many of the aforementioned reports.

Given the aforementioned literature, careful monitoring will be needed with sargramostim use in the COVID-19 setting, particularly as late stages of COVID-19 are thought to be driven by host overactive immunity rather than high viral load[43]. GM-CSF administration can induce flu-like symptoms, leukocytosis and capillary leak syndrome[67], therefore posing the potential risk of exacerbating the SARS-CoV-2-induced hyperinflammatory response. BALF analyses of patients with COVID-19 have shown that alveolar macrophages are depleted in patients with severe COVID-19 (REFS[46]), indicating perhaps that GM-CSF administration may be more beneficial in patients with earlier-stage COVID-19. Indeed, the COVID-19 trials assessing GM-CSF administration exclude patients with ferritin levels greater than 2,000 μg ml^{-1} (consistent with ongoing HLH) and thus may treat patients before they progress to an overt hyperinflammatory phenotype.

Rationale for neutralizing GM-CSF in COVID-19. Anti-inflammatory therapies have attracted great interest in COVID-19, and an immunomodulatory agent that is able to prevent or reduce the disease-driving hyperactive immune response could be a beneficial therapy for late-stage COVID-19 (REF.[25]). In COVID-19 and other coronavirus-mediated diseases, pathogenic myeloid cell overactivation is thought to be an important mediator of tissue damage, hypercoagulation and the cytokine storm[44,72]. BALF analyses from patients with mild or severe COVID-19 showed that patients with severe COVID-19 experienced significant lung infiltration by circulating inflammatory monocyte-derived macrophages[46]. Due to its role as a myeloid cell growth factor and pro-inflammatory cytokine, GM-CSF may be a key driver of the immunopathological sequelae of COVID-19.

Although virtually undetectable in the circulation of healthy individuals[14], GM-CSF was recently noted as being upregulated in the serum of a subset of patients with COVID-19 (REF.[73]). It was reported that the percentages of GM-CSF-expressing CD4$^+$ T cells, CD8$^+$ T cells, natural killer cells and B cells were significantly higher in the blood of patients with COVID-19 who were admitted to an intensive care unit (ICU) than in healthy controls[1]. This pan-cellular observation was not seen with IL-6 and TNF expression in the respective populations. Furthermore, a GM-CSF$^+$IFNγ$^+$CD4$^+$ T cell signature, which is associated with GvHD[31] and autoimmune arthritis[26], encephalomyelitis[74] and diabetes[75], was found in the peripheral blood of the patients in the ICU. These T cell responses were accompanied by a significant increase in the numbers of CD14$^+$CD16$^+$ inflammatory monocytes, and a high percentage of monocytes secreted GM-CSF and IL-6 (REF.[1]). The reported immunological changes appeared to be more pronounced in patients admitted to an ICU than in those who did not require ICU care and thus appear to correlate with clinical severity. Similarly, a study in patients with sepsis demonstrated that an increased percentage of circulating GM-CSF-producing T_H cells is predictive of poor outcome and is correlated with IL-1 and IL-6 expression; these cells exhibited a memory phenotype and were reported to be mediators of dysfunctional neutrophil activity[38]. However, given the role of GM-CSF in pathogen clearance and lung repair, it is important to consider that GM-CSF levels may be elevated as a compensatory mechanism or as a background consequence of increased COVID-19 severity. Further studies are therefore needed to determine whether increased production of GM-CSF in patients with COVID-19 represents a physiological response to infection or a pathogenic driver of disease.

We, along with others[1,72], suggest that in patients with COVID-19, dysregulated GM-CSF expression could induce overactivation of myeloid cells that secrete pro-inflammatory mediators and destructively infiltrate tissue, such as

the lungs and potentially even the heart and the nervous system. This suggestion is consistent with the disease-driving mechanism of action of GM-CSF proposed in many preclinical models with pathologies similar to that of late stages of COVID-19, including models of chimeric antigen receptor (CAR) T cell-related CRS and neurotoxicity[76], GvHD-associated CRS[31], septic shock[77,78], neuroinflammatory disease[21], inflammatory lung conditions[71,79–85] and acute cardiovascular diseases (myocarditis[86], myocardial infarction[33] and vasculitis[87]). Therapeutic inhibition of GM-CSF has shown benefit (including survival advantages) in all of these preclinical models by decreasing the production of multiple pro-inflammatory cytokines/chemokines and reducing tissue infiltration by inflammatory immune cells[2,3]. Of note, a recent report described an outbreak of 'Kawasaki-like' disease in SARS-CoV-2-infected children[88], and GM-CSF neutralization via mAb in a mouse model of Kawasaki disease led to significant reductions in disease incidence and severity[89]. With respect to the lung, systemic monoclonal anti-GM-CSF administration after intranasal lipopolysaccharide challenge in mice reduced the lung accumulation of myeloid cells in a dose-dependent manner[79]. A similar benefit was achieved with the use of GM-CSF neutralization to treat inflamed lungs in multiple other mouse studies[80–83]. A phase II trial of monoclonal anti-GM-CSF administration in patients with asthma demonstrated no benefit in the overall population but statistically significant improvement versus placebo on the primary outcome measure in prespecified subgroups[32].

In mouse models of SARS-CoV infection, GM-CSF was proposed as a mediator of the lethal SARS-CoV-induced infiltration of inflammatory monocytes/macrophages into the lungs[90]. GM-CSF was upregulated before all other cytokines (IL-6, TNF and IFNβ) and chemokines (CCL2, CCL7 and CCL12) that were measured, indicating that GM-CSF might be involved in the initiation of this immunopathological process. In these studies, genetically modified mice (*Ifnar*$^{-/-}$ mice, which cannot respond to type I interferon) did not experience the early upregulation of GM-CSF and were protected from the cellular infiltration and death[90]. Experimental depletion of inflammatory monocytes and macrophages resulted in significantly reduced morbidity and mortality (100% survival out to ~2 weeks versus ~20–40% in controls) and increased numbers of virus-specific T cells in the lungs, demonstrating the therapeutic potential of downregulating inflammatory myeloid cells in coronavirus infections[90].

Together, these data suggest that the use of mAbs to GM-CSF or GM-CSFR might be a promising therapeutic strategy for curbing the hyperactive host immune response observed in COVID-19. A number of large clinical trials in patients with COVID-19 are currently assessing similar immunomodulatory strategies. These include IL-6 targeting via sarilumab or tocilizumab, the latter of which is FDA-approved for CAR T cell-related CRS[72], and IL-1 blockade with anakinra or canakinumab[72,91]. Recently, a data monitoring committee analysis of an ongoing phase II/III randomized controlled trial of sarilumab showed a large reduction in C-reactive protein levels and an increase versus placebo on ventilator-free survival in 'critical' patients with COVID-19 (requiring high-flow oxygenation, mechanical ventilation or ICU care at study entry) ($N = 44$ receiving placebo, $N = 88$ receiving high-dose sarilumab therapy, no P values reported)[92]. The data monitoring committee recommended stopping the assessment of low-dose treatment, as well as discontinuing the enrolment of patients with "severe" disease (requiring supplemental oxygen without mechanical or high-flow oxygenation) and patients exhibiting multiorgan system dysfunction, demonstrating the importance of timing and dose strength for the use of immunomodulatory biologics in COVID-19 (REF.[92]). The careful assessment of the designs and results of these types of cytokine-targeting mAb clinical trial will be important for setting expectations and implementing amendments during the ongoing GM-CSF-targeted mAb clinical trials in patients with COVID-19.

Because GM-CSF can stimulate the expression of IL-1, IL-6, TNF and other pro-inflammatory cytokines and chemokines, a GM-CSF-targeting strategy might have broader effects than other immunomodulatory approaches when one is seeking to therapeutically dampen overactive immune responses. This hypothesis is supported by data from clinical trials in which GM-CSF-targeted therapy was shown to be efficacious in patients with rheumatoid arthritis who were unresponsive to TNF-targeted therapy[93,94]. In a head-to-head study comparing GM-CSF blockade with monoclonal anti-TNF therapy in patients with rheumatoid arthritis, GM-CSF blockade induced a sustained reduction in the levels of markers of inflammation, such as C-reactive protein and IL-6, whereas monoclonal anti-TNF therapy did not in the particular population under study[40]. Even given the benefits of tocilizumab in CRS, it has been speculated that patients can become refractory owing to early and sustained upregulation of GM-CSF[76,95,96], and clinical trials are ongoing or planned to assess the benefit of GM-CSF-targeting mAbs in CAR T cell-related CRS and in CRS associated with GvHD[4–6].

In summary, these data suggest that GM-CSF can have a master regulatory effect on cytokine expression and myeloid cell-mediated hyperinflammation, including in the lung. Many of the preclinical and clinical data from the GM-CSF-targeting mAb therapeutic class come from inflammatory disorders not caused by a viral pathogen, making extrapolation to COVID-19 difficult. However, as mentioned earlier, late stages of COVID-19 appear to be driven not by active viral replication and cell lysis but instead by host immunopathology — particularly myeloid cell immunopathology — that is similar to many aspects of these disorders[43,72]. Thus, the putative pathogenic role of GM-CSF in immune overactivation across many studies provides a rationale for the initiation of the ongoing randomized controlled trials using GM-CSF-targeting mAbs for the treatment of patients with COVID-19 (TABLE 1).

Risks associated with GM-CSF inhibition in COVID-19. Given the homeostatic role of GM-CSF in the lung, blocking GM-CSF action in patients with COVID-19 comes with the potential risks of compromising alveolar macrophage function and hindering pathogen clearance. As with any anti-inflammatory approach under investigation in COVID-19, close monitoring for evidence of viral exacerbation will be needed. Importantly, mAbs to GM-CSF and GM-CSFR have demonstrated a strong safety profile to date across more than 1,000 patients treated in multiple phase II trials[2], including a long-term safety study where patients were receiving the therapy for a median of 2.5 years[97]. Although secondary infections could have been expected (as can be observed in patients receiving TNF- or IL-6-targeted therapy), no increase in tuberculosis and other serious infections has so far been noted[2]. While PAP is of theoretical concern, no patient has developed this disease in any monoclonal anti-GM-CSF or monoclonal anti-GM-CSFR trial to date. It has been hypothesized that primary PAP can develop only from dramatic and sustained GM-CSF

neutralization by polyclonal antibodies (for example, autoantibodies)[98].

In the COVID-19 setting, therapeutic intervention will occur over a short time frame (likely 2 weeks or less), lessening the risk of lung toxicity. Furthermore, the timing of mAb administration may be very important. Although GM-CSF could be beneficial for maintaining alveolar macrophage function during the viral assault in the early disease phase, neutralizing GM-CSF may be able to reduce the primary pathology of the cytokine storm and myeloid cell-induced lung destruction in later disease stages.

mAbs to GM-CSF and GM-CSFR in development to treat COVID-19. A number of clinical trials of systemically administered mAbs to GM-CSF or GM-CSFR have been completed or are ongoing for inflammatory/autoimmune conditions; recently, six companies initiated clinical studies assessing these mAbs for the treatment of COVID-19 (TABLE 1). Encouraging data were obtained from an open-label cohort study of patients with COVID-19 treated with the GM-CSFR mAb mavrilimumab ($N = 13$), compared with a matched contemporaneous untreated control group ($N = 26$)[6]. Benefits in the mavrilimumab-treated group were reported across multiple clinically relevant end points, including time to hospital discharge and mortality; mavrilimumab was observed to be well tolerated in all patients, with no infusion reactions[6]. However, these findings need to be confirmed in larger studies that are placebo controlled.

As of 28 May 2020, six randomized, double-blind, placebo-controlled trials were ongoing for GM-CSF-targeting mAbs in COVID-19 (TABLE 1). The lenzilumab trial ($N = 238$, NCT04351152) excludes patients with ARDS, and the mavrilimumab trials ($N = 60$, NCT04399980; $N = 50$, NCT04397497) exclude patients receiving mechanical ventilation at the time of randomization. By contrast, the otilimab ($N = 800$, NCT04376684), gimsilumab ($N = 270$, NCT04351243), and TMJ2 ($N = 144$, NCT04341116) trials allow inclusion of these patients. The differing target patient populations in these studies should indicate whether targeting GM-CSF may be effective at early and/or late stages of COVID-19. Of note, there is expected to be little difference between targeting the GM-CSF ligand versus the receptor because both strategies block the same interaction. Indeed, preclinical and clinical trial data in rheumatoid arthritis have shown similar benefits for these two approaches[2].

Conclusion

We have provided the rationale and risks for both therapeutically administering and inhibiting GM-CSF in COVID-19. Given the pleiotropic roles of GM-CSF in lung health, host defence and inflammation, care should be taken with respect to dose, route and timing of administration for each therapeutic approach. GM-CSF administration in patients with COVID-19 may improve lung function by strengthening the alveolar wall and enhancing viral clearance, and this approach may thus provide particular benefit in early stages of COVID-19. By contrast, GM-CSF or GM-CSFR blockade could be a beneficial treatment for the cytokine storm and inflammatory myeloid cell tissue infiltration associated with moderate-to-severe COVID-19. The GM-CSF blockade strategy may have broad immunomodulatory effects given that it could affect the secretion of multiple pro-inflammatory cytokines and chemokines by myeloid cells. In our view, the GM-CSF-based therapies are worthwhile investigational approaches during the urgent global search for effective COVID-19 therapeutics.

Frederick M. Lang[1], *Kevin M.-C. Lee*[2], *John R. Teijaro*[3], *Burkhard Becher*[4] *and John A. Hamilton*[2,5]✉

[1]*Roivant Sciences Inc., New York, NY, USA.*

[2]*Department of Medicine, Royal Melbourne Hospital, The University of Melbourne, Parkville, Melbourne, Victoria, Australia.*

[3]*Department of Immunology and Microbiology, Scripps Research Institute, La Jolla, CA, USA.*

[4]*Institute of Experimental Immunology, University of Zurich, Zurich, Switzerland.*

[5]*Australian Institute for Musculoskeletal Science, The University of Melbourne and Western Health, St Albans, Melbourne, Victoria, Australia.*

✉*e-mail: jahami@unimelb.edu.au*

https://doi.org/10.1038/s41577-020-0357-7

Published online 23 June 2020

1. Zhou, Y. et al. Pathogenic T cells and inflammatory monocytes incite inflammatory storm in severe COVID-19 patients. *Natl Sci. Rev.* https://doi.org/10.1093/nsr/nwaa041 (2020).
2. Hamilton, J. A. GM-CSF in inflammation. *J. Exp. Med.* **217**, e20190945 (2020).
3. Hamilton, J. A., Cook, A. D. & Tak, P. P. Anti-colony-stimulating factor therapies for inflammatory and autoimmune diseases. *Nat. Rev. Drug. Discov.* **16**, 53–70 (2016).
4. Humanigen. FDA approves initiation of Humanigen's phase III study of lenzilumab in COVID-19 patients. *Humanigen* https://www.humanigen.com/press/FDA-Approves-Initiation-of-Humanigen%E2%80%99s-Phase-III-Study-of-Lenzilumab-in-COVID-19-Patients (2020).
5. I-Mab Biopharma. I-Mab announces IND clearance from FDA for TJM2 to treat cytokine release syndrome (CRS) associated with severe coronavirus disease 19 (COVID-19). *I-Mab Biopharma* http://www.i-mabbiopharma.com/en/article-517.aspx (2020).
6. Kiniksa Pharmaceuticals. Kiniksa reports data for mavrilimumab in COVID-19 pneumonia and hyperinflammation and for vixarelimab in diseases characterized by chronic pruritus. *Kiniksa* https://investors.kiniksa.com/news-releases/news-release-details/kiniksa-reports-data-mavrilimumab-covid-19-pneumonia-and (2020).
7. Izana Bioscience. Initiation of two-centre compassionate use study involving namilumab in the treatment of individual patients with rapidly worsening COVID-19 infection in Italy. *Izana Bioscience* https://izanabio.com/initiation-of-two-centre-compassionate-use-study-involving-namilumab-in-the-treatment-of-individual-patients-with-rapidly-worsening-covid-19-infection-in-italy/ (2020).
8. Roivant Sciences. Roivant doses first patient in pivotal BREATHE clinical trial evaluating gimsilumab in COVID-19 patients for the prevention and treatment of acute respiratory distress syndrome. *Roivant* https://roivant.com/roivant-doses-first-patient-in-pivotal-breathe-clinical-trial-evaluating-gimsilumab-in-covid-19-patients-for-the-prevention-and-treatment-of-acute-respiratory-distress-syndrome/ (2020).
9. Adams B. GSK taps experimental arthritis antibody to calm the cytokine storm hitting COVID-19 patients. *FierceBiotech*. https://www.fiercebiotech.com/biotech/gsk-taps-experimental-arthritis-antibody-to-calm-cytokine-storm-hitting-covid-19-patients (2020).
10. Wiktor-Jedrzejczak, W. et al. Total absence of colony-stimulating factor 1 in the macrophage-deficient osteopetrotic (Op/Op) mouse. *Proc. Natl Acad. Sci. USA* **87**, 4828–4832 (1990).
11. Lieschke, G. J. et al. Mice lacking granulocyte colony-stimulating factor have chronic neutropenia, granulocyte and macrophage progenitor cell deficiency, and impaired neutrophil mobilization. *Blood* **84**, 1737–1746 (1994).
12. Dai, X. M. et al. Targeted disruption of the mouse colony-stimulating factor 1 receptor gene results in osteopetrosis, mononuclear phagocyte deficiency, increased primitive progenitor cell frequencies, and reproductive defects. *Blood* **99**, 111–120 (2002).
13. Stanley, E. et al. Granulocyte/macrophage colony-stimulating factor-deficient mice show no major perturbation of hematopoiesis but develop a characteristic pulmonary pathology. *Proc. Natl Acad. Sci. USA* **91**, 5592–5596 (1994).
14. Becher, B., Tugues, S. & Greter, M. GM-CSF: from growth factor to central mediator of tissue inflammation. *Immunity* **45**, 963–973 (2016).
15. Guilliams, M. et al. Alveolar macrophages develop from fetal monocytes that differentiate into long-lived cells in the first week of life via GM-CSF. *J. Exp. Med.* **210**, 1977–1992 (2013).
16. Trapnell, B. C. et al. Pulmonary alveolar proteinosis. *Nat. Rev. Dis. Prim.* **7**, 16 (2019).
17. Uchida, K. et al. GM-CSF autoantibodies and neutrophil dysfunction in pulmonary alveolar proteinosis. *N. Engl. J. Med.* **356**, 567–579 (2007).
18. Greter, M. et al. GM-CSF controls nonlymphoid tissue dendritic cell homeostasis but is dispensable for the differentiation of inflammatory dendritic cells. *Immunity* **36**, 1031–1046 (2012).
19. Unkel, B. et al. Alveolar epithelial cells orchestrate DC function in murine viral pneumonia. *J. Clin. Invest.* **122**, 3652–3664 (2012).
20. Zhang, J. et al. A novel subset of helper T cells promotes immune responses by secreting GM-CSF. *Cell Death Differ.* **20**, 1731–1741 (2013).
21. Croxford, A. L., Spath, S. & Becher, B. GM-CSF in neuroinflammation: licensing myeloid cells for tissue damage. *Trends Immunol.* **36**, 651–662 (2015).
22. Komuczki, J. et al. Fate-mapping of GM-CSF expression identifies a discrete subset of inflammation-driving T helper cells regulated by cytokines IL-23 and IL-1β. *Immunity* **50**, 1289–1304 (2019).
23. Cao, Y. et al. Functional inflammatory profiles distinguish myelin-reactive T cells from patients with multiple sclerosis. *Sci. Transl Med.* **7**, 287ra74 (2015).
24. Feldmann, M. et al. Trials of anti-tumour necrosis factor therapy for COVID-19 are urgently needed. *Lancet* **395**, 1407–1409 (2020).
25. Mehta, P. et al. COVID-19: consider cytokine storm syndromes and immunosuppression. *Lancet* **395**, 1033–1034 (2020).
26. Reynolds, G. et al. Synovial CD4+ T-cell-derived GM-CSF supports the differentiation of an inflammatory dendritic cell population in rheumatoid arthritis. *Ann. Rheum. Dis.* **75**, 899–907 (2016).
27. Reghunathan, R. et al. Expression profile of immune response genes in patients with severe acute respiratory syndrome. *BMC Immunol.* **6**, 2 (2005).
28. Matute-Bello, G. et al. Neutrophil apoptosis in the acute respiratory distress syndrome. *Am. J. Respir. Crit. Care Med.* **156**, 1969–1977 (1997).

29. Ahmed, O. CAR-T-cell neurotoxicity: hope is on the horizon. *Blood* **133**, 2114–2116 (2019).
30. Gupta, S. & Weitzman, S. Primary and secondary hemophagocytic lymphohistiocytosis: clinical features, pathogenesis and therapy. *Expert Rev. Clin. Immunol.* **6**, 137–154 (2010).
31. Tugues, S. et al. Graft-versus-host disease, but not graft-versus-leukemia immunity, is mediated by GM-CSF-licensed myeloid cells. *Sci. Transl Med.* **10**, eaat8410 (2018).
32. Molfino, N. A. et al. Phase 2, randomised placebo-controlled trial to evaluate the efficacy and safety of an anti-GM-CSF antibody (KB003) in patients with inadequately controlled asthma. *BMJ Open* **6**, e00709 (2016).
33. Anzai, A. et al. The infarcted myocardium solicits GM-CSF for the detrimental oversupply of inflammatory leukocytes. *J. Exp. Med.* **214**, 3293–3310 (2017).
34. Chen, G. et al. Sca-1$^+$ cardiac fibroblasts promote development of heart failure. *Eur. J. Immunol.* **48**, 1522–1538 (2018).
35. Cid, M. C. et al. GM-CSF pathway signature identified in temporal artery biopsies of patients with giant cell arteritis [Abstract 2689]. *ACR Meeting Abstracts* https://acrabstracts.org/abstract/gm-csf-pathway-signature-identified-in-temporal-artery-biopsies-of-patients-with-giant-cell-arteritis/ (2019).
36. Codarri, L. et al. RORγt drives production of the cytokine GM-CSF in helper T cells, which is essential for the effector phase of autoimmune neuroinflammation. *Nat. Immunol.* **12**, 560–570 (2011).
37. Spath, S. et al. Dysregulation of the cytokine GM-CSF induces spontaneous phagocyte invasion and immunopathology in the central nervous system. *Immunity* **46**, 245–260 (2017).
38. Huang, H. et al. High levels of circulating GM-CSF$^+$CD4$^+$ T cells are predictive of poor outcomes in sepsis patients: a prospective cohort study. *Cell Mol. Immunol.* **16**, 602–610 (2019).
39. Marinoni, B., Ceribelli, A., Massarotti, M. S. & Selmi, C. The Th17 axis in psoriatic disease: pathogenetic and therapeutic implications. *Auto. Immun. Highlights* **5**, 9–19 (2014).
40. Guo, X. et al. Pharmacodynamic biomarkers and differential effects of TNF- and GM-CSF-targeting biologics in rheumatoid arthritis. *Int. J. Rheum. Dis.* **22**, 646–653 (2019).
41. Wu, Z. & McGoogan, J. M. Characteristics of and important lessons from the coronavirus disease 2019 (COVID-19) outbreak in China: summary of a report of 72314 cases from the Chinese Center for Disease Control and Prevention. *JAMA* **323**, 1239–1242 (2020).
42. Channappanavar, R. & Perlman, S. Pathogenic human coronavirus infections: causes and consequences of cytokine storm and immunopathology. *Semin. Immunopathol.* **39**, 529–539 (2017).
43. Siddiqi, H. K. & Mehra, M. R. COVID-19 illness in native and immunosuppressed states: a clinical-therapeutic staging proposal. *J. Heart Lung Transplant.* **39**, 405–407 (2020).
44. Barnes, B. J. et al. Targeting potential drivers of COVID-19: neutrophil extracellular traps. *J. Exp. Med.* **217**, e20200652 (2020).
45. Giamarellos-Bourboulis, E. J. et al. Complex immune dysregulation in COVID-19 patients with severe respiratory failure. *Cell* https://doi.org/10.1016/j.chom.2020.04.009 (2020).
46. Liao, M. et al. Single-cell landscape of bronchoalveolar immune cells in patients with COVID-19. *Nat. Med.* https://doi.org/10.1038/s41591-020-0901-9 (2020).
47. Moore, J. B. & June, C. H. Cytokine release syndrome in severe COVID-19. *Science* **368**, 473–474 (2020).
48. Guo, T. et al. Cardiovascular implications of fatal outcomes of patients with coronavirus disease 2019 (COVID-19). *JAMA Cardiol.* https://doi.org/10.1001/jamacardio.2020.1017 (2020).
49. Troyer, E. A., Kohn, J. N. & Hong, S. Are we facing a crashing wave of neuropsychiatric sequelae of COVID-19? Neuropsychiatric symptoms and potential immunologic mechanisms. *Brain Behav. Immun.* https://doi.org/10.1016/j.bbi.2020.04.027 (2020).
50. Rosler, B. & Herold, S. Lung epithelial GM-CSF improves host defense function and epithelial repair in influenza virus pneumonia-a new therapeutic strategy? *Mol. Cell Pediatr.* **3**, 29 (2016).
51. Paine, R. III. et al. Transgenic overexpression of granulocyte macrophage-colony stimulating factor in the lung prevents hyperoxic lung injury. *Am. J. Pathol.* **163**, 2397–2406 (2003).
52. Baleeiro, C. E. et al. GM-CSF and the impaired pulmonary innate immune response following hyperoxic stress. *Am. J. Physiol. Lung Cell Mol. Physiol.* **291**, L1246–L1255 (2006).
53. Matute-Bello, G. et al. Modulation of neutrophil apoptosis by granulocyte colony-stimulating factor and granulocyte/macrophage colony-stimulating factor during the course of acute respiratory distress syndrome. *Crit. Care Med.* **28**, 1–7 (2000).
54. Paine, R. III. et al. A randomized trial of recombinant human GM-CSF for patients with acute lung injury. *Crit. Care Med.* **40**, 90–97 (2012).
55. Herold, S. et al. Inhaled granulocyte/macrophage colony-stimulating factor as treatment of pneumonia-associated acute respiratory distress syndrome. *Am. J. Respir. Crit. Care Med.* **189**, 609–611 (2014).
56. Subramaniam, R. et al. Delivery of GM-CSF to protect against influenza pneumonia. *PLoS One* **10**, e0124593 (2015).
57. Sever-Chroneos, Z. et al. GM-CSF modulates pulmonary resistance to influenza A infection. *Antivir. Res.* **92**, 319–328 (2011).
58. Steinwede, K. et al. Local delivery of GM-CSF protects mice from lethal pneumococcal pneumonia. *J. Immunol.* **187**, 5346–5356 (2011).
59. Standiford, L. R. et al. TLR4-dependent GM-CSF protects against lung injury in Gram-negative bacterial pneumonia. *Am. J. Physiol. Lung Cell Mol. Physiol.* **302**, L447–L454 (2012).
60. Huang, H., Li, H., Zhou, P. & Ju, D. Protective effects of recombinant human granulocyte macrophage colony stimulating factor on H1N1 influenza virus-induced pneumonia in mice. *Cytokine* **51**, 151–157 (2010).
61. Halstead, E. S. et al. GM-CSF overexpression after influenza a virus infection prevents mortality and moderates M1-like airway monocyte/macrophage polarization. *Respir. Res.* **5**, 3 (2018).
62. Umstead, T. M. et al. Lower respiratory tract delivery, airway clearance, and preclinical efficacy of inhaled GM-CSF in a postinfluenza pneumococcal pneumonia model. *Am. J. Physiol. Lung Cell Mol. Physiol.* **318**, L571–L579 (2020).
63. Ballinger, M. N. et al. Role of granulocyte macrophage colony-stimulating factor during gram-negative lung infection with Pseudomonas aeruginosa. *Am. J. Respir. Cell Mol. Biol.* **34**, 766–774 (2006).
64. Cakarova, L. et al. Macrophage tumor necrosis factor-alpha induces epithelial expression of granulocyte-macrophage colony-stimulating factor: impact on alveolar epithelial repair. *Am. J. Respir. Crit. Care Med.* **180**, 521–532 (2009).
65. Huffman Reed, J. A. et al. GM-CSF enhances lung growth and causes alveolar type II epithelial cell hyperplasia in transgenic mice. *Am. J. Physiol.* **273**, L715–L725 (1997).
66. Partner Therapeutics. Partner Therapeutics announces initiation of clinical trial to evaluate Leukine® in respiratory illness in patients with COVID-19 at Singapore General Hospital. *Partner Therapeutics* https://www.partnertx.com/partner-therapeutics-announces-initiation-of-clinical-trial-to-evaluate-leukine-in-respiratory-illness-in-patients-with-covid-19-at-singapore-general-hospital/ (2020).
67. Sanofi-Aventis. Leukine® (sargramostim) package insert. *FDA* https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/103362s5237lbl.pdf (2017).
68. Summers, C. et al. Pulmonary retention of primed neutrophils: a novel protective host response, which is impaired in the acute respiratory distress syndrome. *Thorax* **69**, 623–629 (2014).
69. Potey, P. M. D., Rossi, A. G., Lucas, C. D. & Dorward, D. A. Neutrophils in the initiation and resolution of acute pulmonary inflammation: understanding biological function and therapeutic potential. *J. Pathol.* **247**, 672–685 (2019).
70. Kudlak, K., DeMuro, J. P., Hanna, A. F. & Brem, H. Acute lung injury following the use of granulocyte-macrophage colony-stimulating factor. *Int. J. Crit. Illn. Inj. Sci.* **3**, 279–281 (2013).
71. De Alessandris, S. et al. Neutrophil GM-CSF receptor dynamics in acute lung injury. *J. Leukoc. Biol.* **105**, 1183–1194 (2019).
72. Merad, M. & Martin, J. C. Pathological inflammation in patients with COVID-19: a key role for monocytes and macrophages. *Nat. Rev. Immunol.* https://doi.org/10.1038/s41577-020-0331-4 (2020).
73. Huang, C. et al. Clinical features of patients with 2019 novel coronavirus in Wuhan, China. *Lancet* **395**, 497–506 (2020).
74. Stienne, C. et al. Foxo3 transcription factor drives pathogenic T helper 1 differentiation by inducing the expression of Eomes. *Immunity* **45**, 774–787 (2016).
75. Oh, S. A. et al. Foxp3-independent mechanism by which TGF-β controls peripheral T cell tolerance. *Proc. Natl Acad. Sci. USA* **114**, E7536–E7544 (2017).
76. Sterner, R. M. et al. GM-CSF inhibition reduces cytokine release syndrome and neuroinflammation but enhances CAR-T cell function in xenografts. *Blood* **133**, 697–709 (2019).
77. Khameneh, H. J., Isa, S. J., Min, L., Nih, F. W. & Ruedl, C. GM-CSF signalling boosts dramatically IL-1 production. *PLoS One* **6**, e23025 (2011).
78. Krebs, J. et al. Intravenous delivery of granulocyte-macrophage colony stimulating factor impairs survival in lipopolysaccharide-induced sepsis. *PLoS One* **14**, e0218602 (2019).
79. Puljic, R. et al. Lipopolysaccharide-induced lung inflammation is inhibited by neutralization of GM-CSF. *Eur. J. Pharmacol.* **557**, 230–235 (2007).
80. Bozinovski, S., Jones, J. E., Vlahos, R., Hamilton, J. A. & Anderson, G. P. Granulocyte/macrophage-colony-stimulating factor (GM-CSF) regulates lung innate immunity to lipopolysaccharide through Akt/Erk activation of NFkappa B and AP-1 in vivo. *J. Biol. Chem.* **277**, 42808–42814 (2002).
81. Willart, M. A. et al. Interleukin-1α controls allergic sensitization to inhaled house dust mite via the epithelial release of GM-CSF and IL-33. *J. Exp. Med.* **209**, 1505–1517 (2012).
82. Shiomi, A. et al. GM-CSF but not IL-17 is critical for the development of severe interstitial lung disease in SKG mice. *J. Immunol.* **193**, 849–859 (2014).
83. Sheih, A., Parks, W. C. & Ziegler, S. F. GM-CSF produced by the airway epithelium is required for sensitization to cockroach allergen. *Mucosal Immunol.* **10**, 705–715 (2017).
84. Kwon, O. C. et al. IL-17A$^+$GM-CSF$^+$ neutrophils are the major infiltrating cells in interstitial lung disease in an autoimmune arthritis model. *Front. Immunol.* **9**, 1544 (2018).
85. Nobs, S. P., Kayhan, M. & Kopf, M. GM-CSF intrinsically controls eosinophil accumulation in the setting of allergic airway inflammation. *J. Allergy Clin. Immunol.* **143**, 1513–1524.e2 (2019).
86. Sonderegger, I. et al. GM-CSF mediates autoimmunity by enhancing IL-6-dependent Th17 cell development and survival. *J. Exp. Med.* **205**, 2281–2294 (2008).
87. Watanabe, R. et al. GM-CSF is a pro-inflammatory cytokine in experimental vasculitis of medium and large arteries [Abstract 1766]. *ACR Meeting Abstracts* https://acrabstracts.org/abstract/gm-csf-is-a-pro-inflammatory-cytokine-in-experimental-vasculitis-of-medium-and-large-arteries/ (2019).
88. Verdoni, L. et al. An outbreak of severe Kawasaki-like disease at the Italian epicentre of the SARS-CoV-2 epidemic: an observational cohort study. *Lancet* https://doi.org/10.1016/S0140-6736(20)31103-X (2020).
89. Stock, A. T., Hansen, J. A., Sleeman, M. A., McKenzie, B. S. & Wicks, I. P. GM-CSF primes cardiac inflammation in a mouse model of Kawasaki disease. *J. Exp. Med.* **213**, 1983–1998 (2016).
90. Channappanavar, R. et al. Dysregulated type I interferon and inflammatory monocyte-macrophage responses cause lethal pneumonia in SARS-CoV-infected mice. *Cell Host Microbe.* **19**, 181–193 (2016).
91. Cavalli, G. et al. Interleukin-1 blockade with high-dose anakinra in patients with COVID-19, acute respiratory distress syndrome, and hyperinflammation: a retrospective cohort study. *Lancet Rheumatol.* https://doi.org/10.1016/S2665-9913(20)30127-2 (2020).
92. Regeneron Pharmaceuticals, Inc. Regeneron and Sanofi provide update on U.S. phase 2/3 adaptive-designed trial of KEVZARA® (sarilumab) in hospitalized COVID-19 patients. *Regeneron* https://newsroom.regeneron.com/news-releases/news-release-details/regeneron-and-sanofi-provide-update-us-phase-23-adaptive (2020).
93. Weinblatt, M. E. et al. A randomized phase IIb study of mavrilimumab and golimumab in rheumatoid arthritis. *Arthritis Rheumatol.* **70**, 49–59 (2018).
94. Taylor, P. C. et al. Efficacy and safety of namilumab, a human monoclonal antibody against granulocyte-macrophage colony-stimulating factor (GM-CSF) ligand in patients with rheumatoid arthritis (RA) with either an inadequate response to background methotrexate therapy or an inadequate response or intolerance to an anti-TNF (tumour necrosis factor) biologic therapy: a randomized, controlled trial. *Arthritis Res. Ther.* **21**, 101 (2019).

95. Ishii, K. et al. Tocilizumab-refractory cytokine release syndrome (CRS) triggered by chimeric antigen receptor (CAR)-transduced T cells may have distinct cytokine profiles compared to typical CRS. *Blood* **128**, 3358 (2016).
96. Sentman, M. L. et al. Mechanisms of acute toxicity in NKG2D chimeric antigen receptor T cell-treated mice. *J. Immunol.* **197**, 4674–4685 (2016).
97. Burmester, G. R. et al. Mavrilimumab, a fully human granulocyte-macrophage colony-stimulating factor receptor α monoclonal antibody: long-term safety and efficacy in patients with rheumatoid arthritis. *Arthritis Rheumatol.* **70**, 679–689 (2018).
98. Piccoli, L. et al. Neutralization and clearance of GM-CSF by autoantibodies in pulmonary alveolar proteinosis. *Nat. Commun.* **6**, 7375 (2015).

Acknowledgements
The authors sincerely thank S. Lowry for his guidance during the ideation for and writing of the manuscript. The authors also thank B. Dorner, A. Berri and T. Lin for their support during the preparation of the manuscript.

Author contributions
All authors contributed significantly to all aspects of the article.

Competing interests
F.M.L. is a full-time employee of Roivant. Roivant is developing gimsilumab, a mAb to GM-CSF under investigation in a phase II clinical trial for the treatment of patients with COVID-19 with lung injury or ARDS. J.R.T., B.B. and J.A.H have received consulting fees from Roivant. The employer of J.A.H. and K.M.-C.L, the University of Melbourne, has licensed patented technology relating to therapeutically targeting GM-CSF to MorphoSys AG, Germany. The employer of B.B., the University of Zurich, holds a patent on the use of neutralizing GM-CSF in acute GvHD following stem cell transplantation and has a license agreement with Humanigen Inc., which is manufacturing such a GM-CSF-neutralizing mAb.

Peer review information
Nature Reviews Immunology thanks M. Dougan and the other, anonymous, reviewer(s) for their contribution to the peer review of this work.

Publisher's note
Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

RELATED LINKS
ClinicalTrials.gov: https://clinicaltrials.gov/